IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

HOFFMANN-LA ROCHE INC.
340 Kingsland Street
Nutley, NJ 07110
USA,

Plaintiff,

v.

HON. JOHN J. DOLL
Acting Under Secretary of Commerce for Intellectual Property and Acting Director of tl United States Patent and Trademark Office.
Office of General Counsel, United States Patent and Trademark Office, P.O. Box 15667, Arlington, VA 22215
Madison Building East, Rm 10B20, 600 Dulany Street, Alexandria, VA 22314,

Defendant.

Plaintiff, Hoffmann-La Roche Inc. ("Hoffmann-La Roche"), for its Complaint against the Honorable John J. Doll, states as follows:

NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent No. 7,442,776 ("the '776 patent") seeking judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '776 patent be changed from 580 days to 841 days.

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedure Act, 5 U.S.C. §§ 701-706.

THE PARTIES

3. Plaintiff Hoffmann-La Roche is a corporation organized under the laws of New Jersey, having a principal place of business at 340 Kingsland Street, Nutley, NJ.

4. Defendant John J. Doll is the Acting Under Secretary of Commerce for Intellectual Property and Acting Director of the United States Patent and Trademark Office ("PTO"), acting in his official capacity. The Director is the head of the PTO and is responsible for superintending or performing all duties required by law with respect to the granting and issuing of patents, and is designated by statute as the official responsible for determining the period of patent term adjustments under 35 U.S.C. § 154.

JURISDICTION AND VENUE

5. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1361, 35 U.S.C. § 154(b)(4)(A), and 5 U.S.C. §§ 701-706.

6. Venue is proper in this district by virtue of 35 U.S.C. § 154(b)(4)(A).

7. This Complaint is being timely filed in accordance with 35 U.S.C. § 154(b)(4)(A).

BACKGROUND

8. David S. F. Young, Susan E. Hahn, and Helen P. Findlay are inventors of the patent application No. 10/810,163 ("the '163 application"), which issued on October 8, 2008 as the '776 patent, entitled "Cancerous Disease Modifying Antibodies". A copy of '776 patent is attached hereto as Exhibit A.

9. Plaintiff Hoffmann-La Roche is the assignee of the '776 patent as evidenced by records in the PTO and is the real party in interest in this case.

10. Section 154(b) of 35 U.S.C. requires that the Director of the PTO grant a patent term adjustment. Specifically, 35 U.S.C. § 154(b)(3)(D) states that "[t]he Director shall proceed to grant the patent after completion of the Director's determination of a patent term adjustment

17. Under 35 U.S.C. § 154(b)(1)(B), the plaintiff is entitled to an additional adjustment of the term of the '776 patent of a period of 445 days, which is the number of days the issue date of the '776 patent exceeds three years from the filing date of the application, up to the June 13, 2008, filing date of the Request for Continued Examination ("B Delay").

18. Title 35, U.S.C. § 154(b)(2)(A) states that "to the extent . . . periods of delay attributable to grounds specified in paragraph [154(b)(1)] overlap, the period of any adjustment granted under this subsections shall not exceed the actual number of days the issuance of the patent was delayed." For the '776 patent, none of the A Delay period overlaps with the B Delay period. Therefore, there is no period of overlap to be excluded from the patent term adjustment.

19. Thus, the total period of PTO delay is 1,025 days, which is the sum of the period of A Delay (580 days) and the period of B Delay (445 days).

20. Under 35 U.S.C. § 154(b)(2)(C), the total period of PTO delay is reduced by the period of applicant delay, which, in this case, is 184 days as determined by the PTO.

21. Accordingly, the correct patent term adjustment under 35 U.S.C. § 154(b)(1) and (2) is 841 days, which is the difference between the total period of PTO delay (1,025 days) and the period of applicant delay (184 days).

22. The defendant's imposition of only 580 days of patent term adjustment for the '776 patent is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and in excess of statutory jurisdiction, authority or limitation.

23. The defendant's determination that the period of the patent term adjustment for the '776 patent is only 580 days is in conflict with this Court's decision in *Wyeth v. Dudas*, 580 F. Supp.2d 138, 88 USPQ2d 1538 (D.D.C. 2008), which explains the proper method for

calculating patent term adjustments under 35 U.S.C. § 154(b). A copy *Wyeth v. Dudas* decision is attached hereto as Exhibit B.

WHEREFORE, Plaintiff respectfully prays that this Court:

A. Issue an Order changing the period of patent term adjustment for the '776 patent from 580 days to 841 days and requiring defendant to alter the term of the '776 patent to reflect the 841-day patent term adjustment; and

B. Grant such other and further relief as the nature of the case may admit or require and as may be just and equitable.

Respectfully submitted,

FISH & RICHARDSON P.C.

Dated: April 24, 2009

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EXHIBIT A

(12) **United States Patent**
Young et al.

(10) **Patent No.: US 7,442,776 B2**
(45) **Date of Patent: Oct. 28, 2008**

(54) **CANCEROUS DISEASE MODIFYING ANTIBODIES**

(76) Inventors: **David S. F. Young**, 33 University Avenue, Suite 2407, Toronto, Ontario (CA) M5J 2S7; **Susan E. Hahn**, 9 Innisfree Court, Toronto, Ontario (CA) M6P 3N7; **Helen P. Findlay**, 205 Glendonwynne Road, Toronto, Ontario (CA) M6P 3E9

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U S.C. 154(b) by 396 days.

(21) Appl. No.: **10/810,163**

(22) Filed: **Mar. 26, 2004**

(65) **Prior Publication Data**

US 2004/0180002 A1 Sep. 16, 2004

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/713,642, filed on Nov. 13, 2003, now Pat. No. 7,256,272, which is a continuation of application No. 09/727,361, filed on Nov. 29, 2000, now Pat. No. 6,657,048, which is a continuation-in-part of application No. 09/415,278, filed on Oct. 8, 1999, now Pat. No. 6,180,357.

(51) **Int. Cl.**
C07K 16/00 (2006.01)

(52) **U.S. Cl.** **530/388.1**; 424/130.1

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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5,750,102	A	5/1998	Eisenbach et al.
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5,783,186	A	7/1998	Arakawa et al.
5,849,876	A	12/1998	Linsley et al.
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5,869,268	A	2/1999	Kudo et al.
6,180,357	B1	1/2001	Young et al.
6,657,048	B2	12/2003	Young et al.

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(Continued)

Primary Examiner—Larry R. Helms
Assistant Examiner—Meera Natarajan
(74) *Attorney, Agent, or Firm*—McHale & Slavin, P.A.

(57) **ABSTRACT**

The present invention relates to a method for producing patient cancerous disease modifying antibodies using a novel paradigm of screening. By segregating the anti-cancer antibodies using cancer cell cytotoxicity as an end point, the process makes possible the production of anti-cancer antibodies for therapeutic and diagnostic purposes. The antibodies can be used in aid of staging and diagnosis of a cancer, and can be used to treat primary tumors and tumor metastases. The anti-cancer antibodies can be conjugated to toxins, enzymes, radioactive compounds, and hematogenous cells.

8 Claims, 4 Drawing Sheets

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FIGURE 1

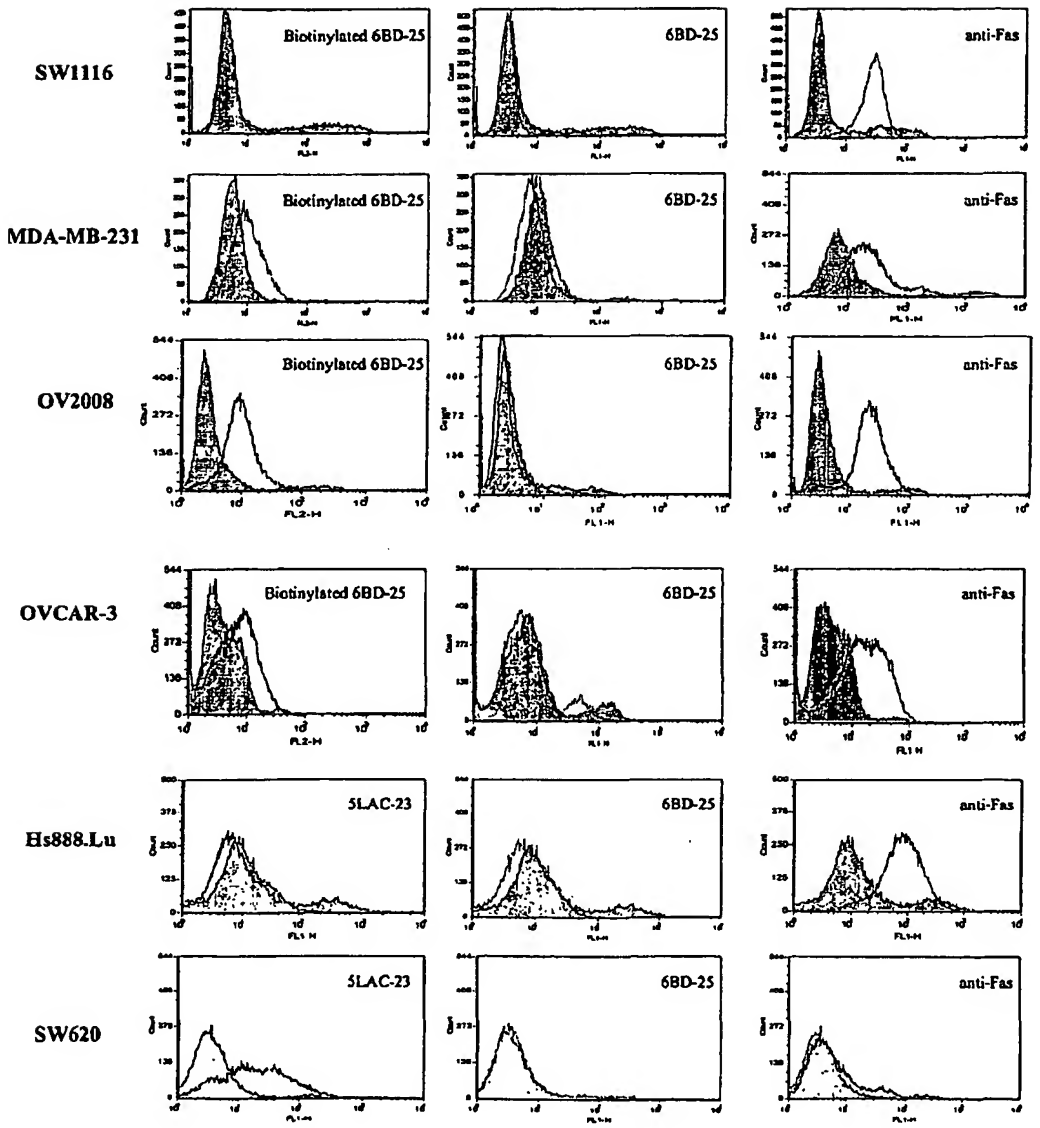

SW1116
MDA-MB-231
OV2008
OVCAR-3
Hs888.Lu
SW620
Biotinylated 6BD-25
6BD-25
anti-Fas
5LAC-23

FIGURE 2

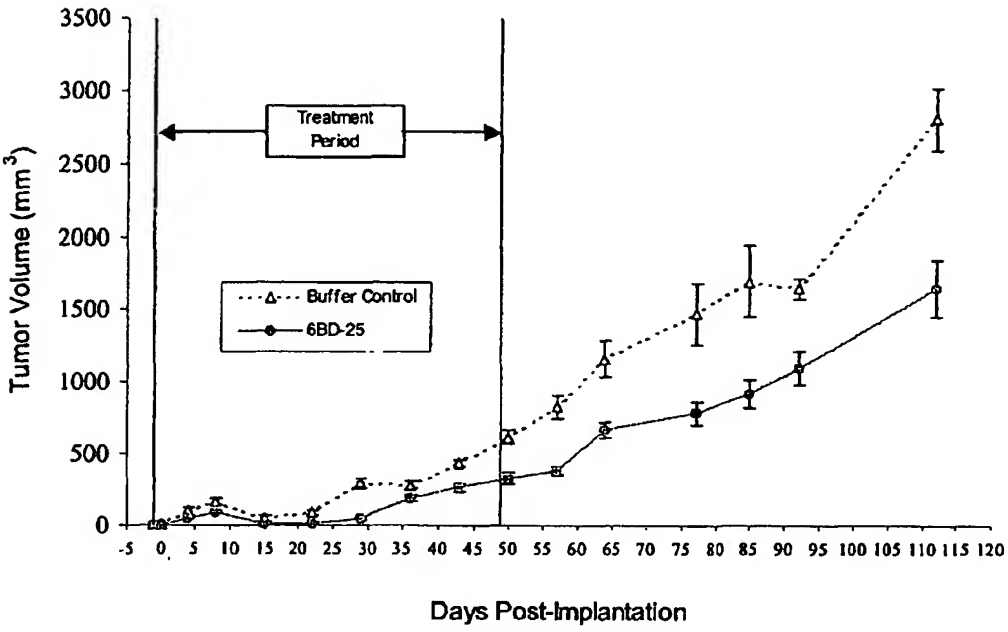

Tumor Volume (mm3)
3500
3000
2500
2000
1500
1000
500
0
Treatment Period
Buffer Control
6BD-25
-5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120
Days Post-Implantation

FIGURE 3

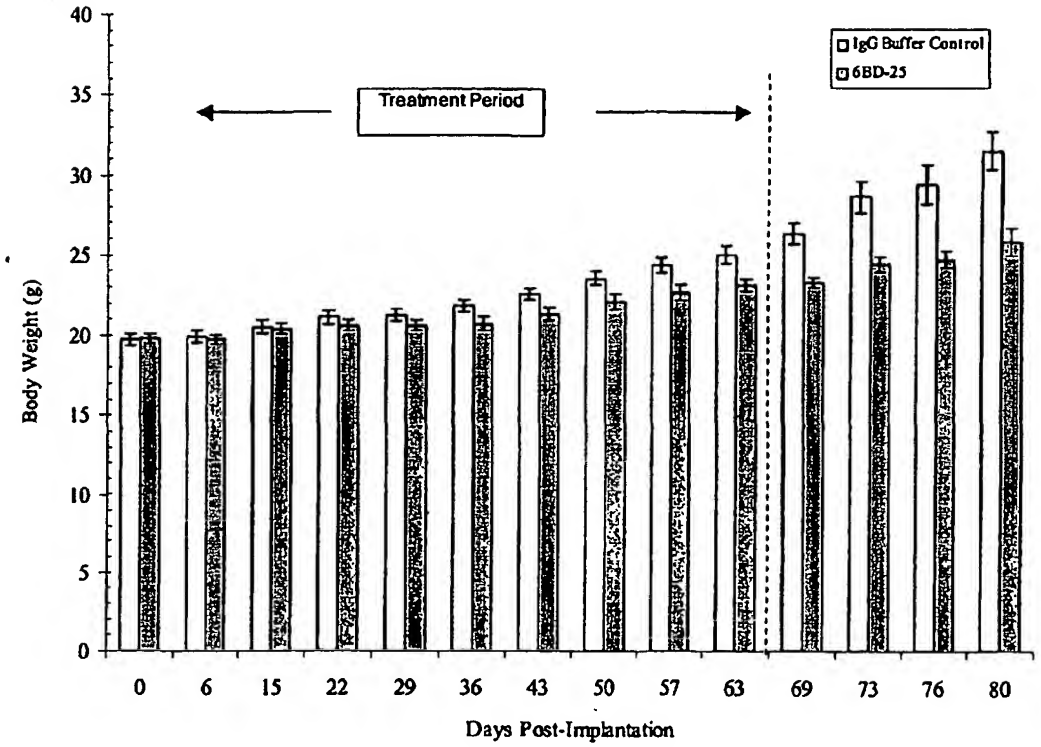
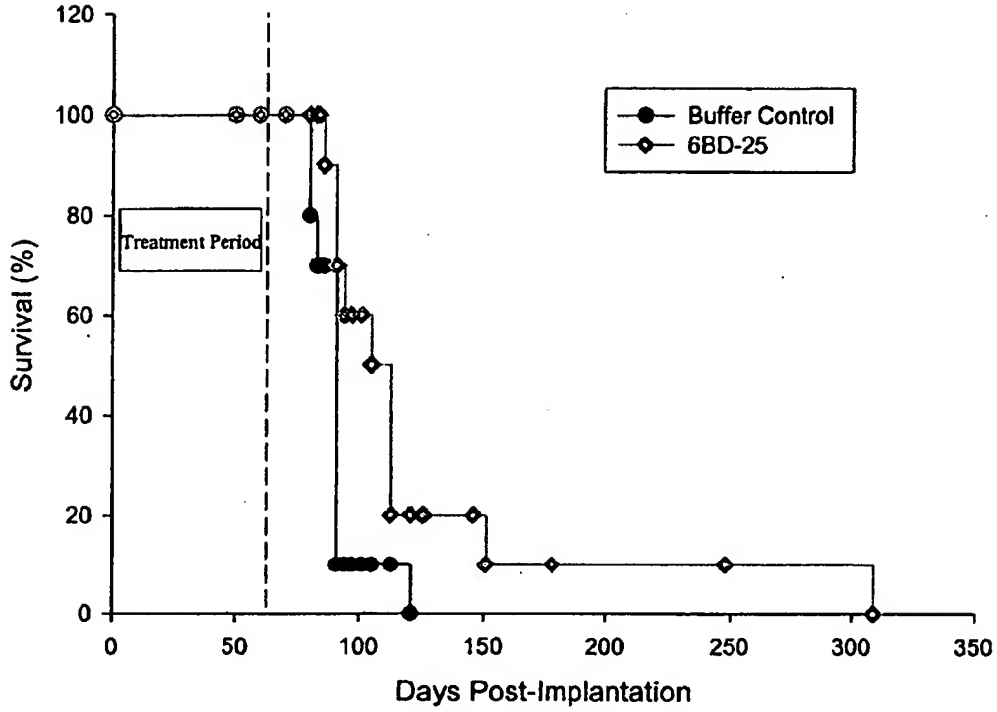

IgG Buffer Control
6BD-25
Treatment Period
Body Weight (g)
40
35
30
25
20
15
10
5
0
0
6
15
22
29
36
43
50
57
63
69
73
76
80
Days Post-Implantation

FIGURE 4


120
100
80
60
40
20
0
Survival (%)
Treatment Period
Buffer Control
6BD-25
0
50
100
150
200
250
300
350
Days Post-Implantation

CANCEROUS DISEASE MODIFYING ANTIBODIES

REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 10/713,642, filed Nov. 13, 2003, now U.S. Pat. No. 7,256,272, issued Aug. 14, 2007, which is a continuation of application Ser. No. 09/727,361, filed Nov. 29, 2000, now U.S. Pat. No. 6,657,048, which is a continuation-in-part of application Ser. No. 09/415,278, filed Oct. 8, 1999, now U.S. Pat. No. 6,180,357 B1, the contents of each of which are herein incorporated by reference.

FIELD OF THE INVENTION

This invention relates to the isolation and production of cancerous disease modifying antibodies (CDMAB) and to the use of these CDMAB in therapeutic and diagnostic processes, optionally in combination with one or more chemotherapeutic agents. The invention further relates to binding assays which utilize the CDMAB of the instant invention.

BACKGROUND OF THE INVENTION

Each individual who presents with cancer is unique and has a cancer that is as different from other cancers as that person's identity. Despite this, current therapy treats all patients with the same type of cancer, at the same stage, in the same way. At least 30 percent of these patients will fail the first line therapy, thus leading to further rounds of treatment and the increased probability of treatment failure, metastases, and ultimately, death. A superior approach to treatment would be the customization of therapy for the particular individual. The only current therapy that lends itself to customization is surgery. Chemotherapy and radiation treatment cannot be tailored to the patient, and in most cases, surgery by itself is inadequate for producing cures.

With the advent of monoclonal antibodies, the possibility of developing methods for customized therapy became more realistic since each antibody can be directed to a single epitope. Furthermore, it is possible to produce a combination of antibodies that are directed to the constellation of epitopes that uniquely define a particular individual's tumor.

Having recognized that a significant difference between cancerous and normal cells is that cancerous cells contain antigens that are specific to transformed cells, the scientific community has long held that monoclonal antibodies can be designed to specifically target transformed cells by binding specifically to these cancer antigens. This has given rise to the belief that monoclonal antibodies can serve as "Magic Bullets" to eliminate cancer cells.

Monoclonal antibodies isolated in accordance with the teachings of the instantly disclosed invention have been shown to modify the cancerous disease process in a manner which is beneficial to the patient, for example by reducing the tumor burden, and will variously be referred to herein as cancerous disease modifying antibodies (CDMAB) or "anti-cancer" antibodies.

At the present time, the cancer patient usually has few options of treatment. The regimented approach to cancer therapy has produced improvements in global survival and morbidity rates. However, to the particular individual, these improved statistics do not necessarily correlate with an improvement in their personal situation.

Thus, if a methodology was put forth which enabled the practitioner to treat each tumor independently of other

patients in the same cohort, this would permit the unique approach of tailoring therapy to just that one person. Such a course of therapy would, ideally, increase the rate of cures, and produce better outcomes, thereby satisfying a long-felt need.

Historically, the use of polyclonal antibodies has been used with limited success in the treatment of human cancers. Lymphomas and leukemias have been treated with human plasma, but there were few prolonged remission or responses. Furthermore, there was a lack of reproducibility and no additional benefit compared to chemotherapy. Solid tumors such as breast cancers, melanomas and renal cell carcinomas have also been treated with human blood, chimpanzee serum, human plasma and horse serum with correspondingly unpredictable and ineffective results.

There have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin. In this trial 37 patients were accessed for responses of which about a quarter had a partial response rate and another half had minor or stable disease progression.

The clinical trials investigating colorectal cancer involve antibodies against both glycoprotein and glycolipid targets. Antibodies such as 17-1A, which has some specificity for adenocarcinomas, has undergone Phase 2 clinical trials in over 60 patients with only 1 patient having a partial response. In other trials, use of 17-1A produced only 1 complete response and 2 minor responses among 52 patients in protocols using additional cyclophosphamide. Other trials involving 17-1A yielded results that were similar. The use of a humanized murine monoclonal antibody initially approved for imaging also did not produce tumor regression. To date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate, and stomach cancers. There has been some limited success in the use of anti-GD3 monoclonal antibodies for melanoma. Thus, it can be seen that despite successful small animal studies that are a prerequisite for human clinical trials, the antibodies that have been tested thus far, have been for the most part, ineffective.

Prior Patents:

U.S. Pat. No. 5,750,102 discloses a process wherein cells from a patient's tumor are transfected with MHC genes which may be cloned from cells or tissue from the patient. These transfected cells are then used to vaccinate the patient.

U.S. Pat. No. 4,861,581 discloses a process comprising the steps of obtaining monoclonal antibodies that are specific to an internal cellular component of neoplastic and normal cells of the mammal but not to external components, labeling the monoclonal antibody, contacting the labeled antibody with tissue of a mammal that has received therapy to kill neoplastic cells, and determining the effectiveness of therapy by measuring the binding of the labeled antibody to the internal cellular component of the degenerating neoplastic cells. In preparing antibodies directed to human intracellular antigens, the patentee recognizes that malignant cells represent a convenient source of such antigens.

U.S. Pat. No. 5,171,665 provides a novel antibody and method for its production. Specifically, the patent teaches formation of a monoclonal antibody which has the property of binding strongly to a protein antigen associated with

human tumors, e.g. those of the colon and lung, while binding to normal cells to a much lesser degree.

U.S. Pat. No. 5,484,596 provides a method of cancer therapy comprising surgically removing tumor tissue from a human cancer patient, treating the tumor tissue to obtain tumor cells, irradiating the tumor cells to be viable but non-tumorigenic, and using these cells to prepare a vaccine for the patient capable of inhibiting recurrence of the primary tumor while simultaneously inhibiting metastases. The patent teaches the development of monoclonal antibodies which are reactive with surface antigens of tumor cells. As set forth at col. 4, lines 45 et seq., the patentees utilize autochthonous tumor cells in the development of monoclonal antibodies expressing active specific immunotherapy in human neoplasia.

U.S. Pat. No. 5,693,763 teaches a glycoprotein antigen characteristic of human carcinomas is not dependent upon the epithelial tissue of origin.

U.S. Pat. No. 5,783,186 is drawn to anti-Her2 antibodies which induce apoptosis in Her2 expressing cells, hybridoma cell lines producing the antibodies, methods of treating cancer using the antibodies and pharmaceutical compositions including said antibodies.

U.S. Pat. No. 5,849,876 describes new hybridoma cell lines for the production of monoclonal antibodies to mucin antigens purified from tumor and non-tumor tissue sources.

U.S. Pat. No. 5,869,268 is drawn to a method for generating a human lymphocyte producing an antibody specific to a desired antigen, a method for producing a monoclonal antibody, as well as monoclonal antibodies produced by the method. The patent is particularly drawn to the production of an anti-HD human monoclonal antibody useful for the diagnosis and treatment of cancers.

U.S. Pat. No. 5,869,045 relates to antibodies, antibody fragments, antibody conjugates and single chain immunotoxins reactive with human carcinoma cells. The mechanism by which these antibodies function is two-fold, in that the molecules are reactive with cell membrane antigens present on the surface of human carcinomas, and further in that the antibodies have the ability to internalize within the carcinoma cells, subsequent to binding, making them especially useful for forming antibody-drug and antibody-toxin conjugates. In their unmodified form the antibodies also manifest cytotoxic properties at specific concentrations.

U.S. Pat. No. 5,780,033 discloses the use of autoantibodies for tumor therapy and prophylaxis. However, this antibody is an anti-nuclear autoantibody from an aged mammal. In this case, the autoantibody is said to be one type of natural antibody found in the immune system. Because the autoantibody comes from "an aged mammal", there is no requirement that the autoantibody actually comes from the patient being treated. In addition the patent discloses natural and monoclonal anti-nuclear autoantibody from an aged mammal, and a hybridoma cell line producing a monoclonal anti-nuclear autoantibody.

SUMMARY OF THE INVENTION

The instant inventors have previously been awarded U.S. Pat. No. 6,180,357, entitled "Individualized Patient Specific Anti-Cancer Antibodies" directed to a process for selecting individually customized anti-cancer antibodies which are useful in treating a cancerous disease. For the purpose of this document, the terms "antibody" and "monoclonal antibody" (mAb) may be used interchangeably and refer to intact immunoglobulins produced by hybridomas (e.g. murine or human), immunoconjugates and, as appropriate, immunoglobulin fragments and recombinant proteins derived from immunoglobulins, such as chimeric and humanized immunoglobulins, F(ab') and $F(ab')_2$ fragments, single-chain antibodies, recombinant immunoglobulin variable regions (Fv)s, fusion proteins etc. For the purpose of this document, the term "tissue sample" is understood to mean at least one cell or an aggregate of cells obtained from a mammal. It is well recognized in the art that some amino acid sequence can be varied in a polypeptide without significant effect on the structure or function of the protein. In the molecular rearrangement of antibodies, modifications in the nucleic or amino acid sequence of the backbone region can generally be tolerated. These include, but are not limited to, substitutions (preferred are conservative substitutions), deletions or additions. Furthermore, it is within the purview of this invention to conjugate standard chemotherapeutic modalities, e.g. radionuclides, with the CDMAB of the instant invention, thereby focusing the use of said chemotherapeutics. The CDMAB can also be conjugated to toxins, cytotoxic moieties, enzymes e.g. biotin conjugated enzymes, or hematogenous cells, thereby forming antibody conjugates. Such conjugated moieties are illustrated herein as conjugated to the monoclonal antibody derived from the hybridoma cell line designated 6BD-25; similar antibody conjugates could be formed utilizing the monoclonal antibody derived from the hybridoma cell line designated 5LAC-23.

This application utilizes the method for producing patient specific anti-cancer antibodies as taught in the '357 patent for isolating hybridoma cell lines which encode for cancerous disease modifying monoclonal antibodies. These antibodies can be made specifically for one tumor and thus make possible the customization of cancer therapy. Within the context of this application, anti-cancer antibodies having either cell-killing (cytotoxic) or cell-growth inhibiting (cytostatic) properties will hereafter be referred to as cytotoxic. These antibodies can be used in aid of staging and diagnosis of a cancer, and can be used to treat tumor metastases.

The prospect of individualized anti-cancer treatment will bring about a change in the way a patient is managed. A likely clinical scenario is that a tumor sample is obtained at the time of presentation, and banked. From this sample, the tumor can be typed from a panel of pre-existing cancerous disease modifying antibodies. The patient will be conventionally staged but the available antibodies can be of use in further staging the patient. The patient can be treated immediately with the existing antibodies and/or a panel of antibodies specific to the tumor can be produced either using the methods outlined herein or through the use of phage display libraries in conjunction with the screening methods herein disclosed. All the antibodies generated will be added to the library of anti-cancer antibodies since there is a possibility that other tumors can bear some of the same epitopes as the one that is being treated. The antibodies produced according to this method may be useful to treat cancerous disease in any number of patients who have cancers that bind to these antibodies.

Using substantially the process of U.S. Pat. No. 6,180,370 and as outlined in U.S. Pat. No. 6,657,048, the mouse monoclonal antibodies 6BD-25 and 5LAC-23 were obtained following immunization of mice with cells from a patient's breast and lung tumor biopsy respectively. The 6BD-25 antigen was initially not detected on a variety of human normal and cancer cell lines by cell ELISA/FACS. After increasing the sensitivity of the assay through conjugation of the 6BD-25 antibodies to biotin, the antigen was detected on the breast cancer cell line MDA-MB-231 and the ovarian cancer cell lines C-13, OVCA-429 and OV2008. The breast cancer cell line Hs574.T was susceptible to the cytotoxic effects of unpu-

rified 6BD-25. The breast cancer cell line MCF-7, the ovarian cancer cell line OVCAR-3 and the colon cancer cell line SW1116 were the only 3 cancer cell lines tested that were susceptible to the cytotoxic effects of purified 6BD-25. Through the use of FACS analysis, the antigen for 5LAC-23 was detected on the SW620 colon cancer cell line and not on any of the other cell lines tested. The breast (Hs574.T), lung (NCI-H661) and skin (A2058) cancer cell line were susceptible to the cytotoxic effects of unpurified 5LAC-23. The ovarian cancer cell line OVCAR-3 was the only cancer cell line tested that was susceptible to the cytotoxic effects of purified 5LAC-23.

The result of 6BD-25 cytotoxicity against OVCAR-3 and SW1116 cells in culture was further extended by its anti-tumor activity towards these cells when transplanted into mice. In an in vivo model of colon cancer, the human SW1116 cells were implanted subcutaneously at the scruff of the neck while for an in vivo model of ovarian cancer, the human OVCAR-3 cells were implanted intraperitoneally. For both models, immunodeficient mice were used as they are incapable of rejecting the human tumor cells due to a lack of certain immune cells. Pre-clinical xenograft tumor models are considered valid predictors of therapeutic efficacy. Xenografts in mice grow as solid tumors developing stroma, central necrosis and neo-vasculature. The tumor cell lines OVCAR-3 and SW1116 have been evaluated as an in vivo xenograft model in immunodeficient mice. The good engraftment or 'take-rate' of the OVCAR-3 and SW1116 tumors and the sensitivity of the tumors to standard chemotherapeutic agents have characterized them as suitable models. The parental cell line and variants of the cell line have been used in xenograft tumor models to evaluate a wide range of therapeutic agents.

In the preventative in vivo model of human colon cancer, 6BD-25 was given to mice one day prior to implantation of tumor cells followed by weekly injections for a period of 7 weeks. 6BD-25 treatment was significantly ($p=0.001$) more effective in suppressing tumor growth during the treatment period than buffer control. At the end of the treatment phase, mice given 6BD-25 had tumors that grew to only 54 percent of the control group. During the post treatment follow-up period, the treatment effects of 6BD-25 were sustained and the mean tumor volume in the treated groups continued to be significantly smaller than controls until the end of the measurement phase ($p=0.002$). 6BD-25 treatment appeared safe, as it did not induce any signs of toxicity, including reduced body weight or other signs of clinical distress. Thus, 6BD-25 treatment was efficacious as it delayed tumor growth compared to the control-treated group in a well-established model of human colon cancer.

Besides the preventative in vivo tumor model of colon cancer, 6BD-25 demonstrated anti-tumor activity against OVCAR-3 cells in a preventative ovarian in vivo tumor model. In this xenograft tumor model, OVCAR-3 ovarian cancer cells were transplanted intraperitoenally into immunodeficient mice with treatment commencing the day after implantation for a total of 10 doses. Treatment with 6BD-25 was compared to a buffer control. Body weight was used as a surrogate measure of tumor progression. Increased body weight is indicative of tumor burden since the weight gain is caused by ascites formation. At day 80 post-implantation (16 days after the end of treatment), the mice in the treatment group had body weights significantly less than the control group ($p=0.002$). There was also a significant survival benefit with treatment of 6BD-25 versus the buffer control ($p<0.02$). Again, 6BD-25 treatment appeared safe, as it did not induce any signs of toxicity or clinical distress. The anti-tumor activity of 6BD-25 and its apparent lack of toxicity make it an attractive anti-cancer therapeutic agent.

In all, this invention teaches the use of the 6BD-25 and 5LAC-23 antigens as targets for therapeutic agents and that when administered, 6BD-25 can reduce the tumor burden in a mammal with a cancer expressing the antigen, and can also lead to prolonged survival of the treated mammal. The efficacy of 6BD-25 treatment in vivo and the concomitant undetectable or low level of antigen expression on the SW1116 and OVCAR-3 cells respectively, illustrates that the level of antigen expression does not necessarily correlate with in vivo efficacy. Furthermore, this invention also teaches that detecting the 6BD-25 and 5LAC-23 antigen in cancerous cells can be useful for the diagnosis, prediction of therapy, and prognosis of mammals bearing tumors that express this antigen.

If a patient is refractory to the initial course of therapy or metastases develop, the process of generating specific antibodies to the tumor can be repeated for re-treatment. Furthermore, the anti-cancer antibodies can be conjugated to red blood cells obtained from that patient and re-infused for treatment of metastases. There have been few effective treatments for metastatic cancer and metastases usually portend a poor outcome resulting in death. However, metastatic cancers are usually well vascularized and the delivery of anti-cancer antibodies by red blood cells can have the effect of concentrating the antibodies at the site of the tumor. Even prior to metastases, most cancer cells are dependent on the host's blood supply for their survival and anti-cancer antibodies conjugated to red blood cells can be effective against in situ tumors as well. Alternatively, the antibodies may be conjugated to other hematogenous cells, e.g. lymphocytes, macrophages, monocytes, natural killer cells, etc.

There are five classes of antibodies and each is associated with a function that is conferred by its heavy chain. It is generally thought that cancer cell killing by naked antibodies are mediated either through antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). For example murine IgM and IgG2a antibodies can activate human complement by binding the C-1 component of the complement system thereby activating the classical pathway of complement activation which can lead to tumor lysis. For human antibodies, the most effective complement-activating antibodies are generally IgM and IgG1. Murine antibodies of the IgG2a and IgG3 isotype are effective at recruiting cytotoxic cells that have Fc receptors which will lead to cell killing by monocytes, macrophages, granulocytes and certain lymphocytes. Human antibodies of both the IgG1 and IgG3 isotype mediate ADCC.

Another possible mechanism of antibody-mediated cancer killing may be through the use of antibodies that function to catalyze the hydrolysis of various chemical bonds in the cell membrane and its associated glycoproteins or glycolipids, so-called catalytic antibodies.

There are two additional mechanisms of antibody-mediated cancer cell killing which are more widely accepted. The first is the use of antibodies as a vaccine to induce the body to produce an immune response against the putative antigen that resides on the cancer cell. The second is the use of antibodies to target growth receptors and interfere with their function or to down regulate that receptor so that its function is effectively lost.

The clinical utility of a cancer drug is based on the benefit of the drug under an acceptable risk profile to the patient. In cancer therapy survival has generally been the most sought after benefit, however there are a number of other well-recognized benefits in addition to prolonging life. These other benefits, where treatment does not adversely affect survival,

include symptom palliation, protection against adverse events, prolongation in time to recurrence or disease-free survival, and prolongation in time to progression. These criteria are generally accepted and regulatory bodies such as the U.S. Food and Drug Administration (F.D.A.) approve drugs that produce these benefits (Hirschfeld et al. Critical Reviews in Oncology/Hematolgy 42:137-143 2002). In addition to these criteria it is well recognized that there are other endpoints that may presage these types of benefits. In part, the accelerated approval process granted by the U.S. F.D.A. acknowledges that there are surrogates that will likely predict patient benefit. As of year-end (2003), there have been sixteen drugs approved under this process, and of these, four have gone on to full approval, i.e., follow-up studies have demonstrated direct patient benefit as predicted by surrogate endpoints. One important endpoint for determining drug effects in solid tumors is the assessment of tumor burden by measuring response to treatment (Therasse et al. Journal of the National Cancer Institute 92(3):205-216 2000). The clinical criteria (RECIST criteria) for such evaluation have been promulgated by Response Evaluation Criteria in Solid Tumors Working Group, a group of international experts in cancer. Drugs with a demonstrated effect on tumor burden, as shown by objective responses according to RECIST criteria, in comparison to the appropriate control group tend to, ultimately, produce direct patient benefit. In the pre-clinical setting tumor burden is generally more straightforward to assess and document. In that pre-clinical studies can be translated to the clinical setting, drugs that produce prolonged survival in pre-clinical models have the greatest anticipated clinical utility. Analogous to producing positive responses to clinical treatment, drugs that reduce tumor burden in the pre-clinical setting may also have significant direct impact on the disease. Although prolongation of survival is the most sought after clinical outcome from cancer drug treatment, there are other benefits that have clinical utility and it is clear that tumor burden reduction, which may correlate to a delay in disease progression, extended survival or both, can also lead to direct benefits and have clinical impact (Eckhardt et al. Developmental Therapeutics: Successes and Failures of Clinical Trial Designs of Targeted Compounds; ASCO Educational Book, 39th Annual Meeting, 2003, pages 209-219).

Accordingly, it is an objective of the invention to utilize a method for producing cancerous disease modifying antibodies from cells derived from a particular individual which are cytotoxic with respect to cancer cells while simultaneously being relatively non-toxic to non-cancerous cells, in order to isolate hybridoma cell lines and the corresponding isolated monoclonal antibodies and antigen binding fragments thereof for which said hybridoma cell lines are encoded.

It is an additional objective of the invention to teach CDMAB and antigen binding fragments thereof.

It is a further objective of the instant invention to produce CDMAB whose cytotoxicity is mediated through ADCC.

It is yet an additional objective of the instant invention to produce CDMAB whose cytotoxicity is mediated through CDC.

It is still a further objective of the instant invention to produce CDMAB whose cytotoxicity is a function of their ability to catalyze hydrolysis of cellular chemical bonds.

A still further objective of the instant invention is to produce CDMAB which are useful in a binding assay for diagnosis, prognosis, and monitoring of cancer.

Other objects and advantages of this invention will become apparent from the following description wherein, by way of illustration and example, certain embodiments of this invention are set forth.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Representative FACS histograms of 6BD-25, 5LAC-23 and anti-Fas (positive control) antibodies directed against several cancer and non-cancer cell lines.

FIG. 2. Effect of 6BD-25 on tumor growth in a preventative SW1116 colon cancer model. The dashed line indicates the period during which the antibody was administered. Data points represent the mean +/−SEM.

FIG. 3. Effect of 6BD-25 on body weight in a preventative OVCAR-3 ovarian cancer model. The dashed line indicates the period during which the antibody was administered. Data points represent the mean +/−SEM.

FIG. 4. Survival of tumor-bearing mice after treatment with 6BD-25 or buffer control. Mice were monitored for survival for over 240 days post-treatment.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLE 1

Hybridoma Production—Hybridoma Cell Lines: 6BD-25 and 5LAC-23

The hybridoma cell lines 6BD-25 and 5LAC-23 were deposited, in accordance with the Budapest Treaty, with the American Type Culture Collection (ATCC), 10801 University Blvd., Manassas, Va. 20110-2209 on Dec. 9, 2003, under Accession Number PTA-5691 and PTA-5690 respectively. In accordance with 37 CFR 1.808, the depositors assure that all restrictions imposed on the availability to the public of the deposited materials will be irrevocably removed upon the granting of a patent. The derivation of the clone, the supernatant and cell ELISA screening of 6BD-25 and 5LAC-23 has previously been described in U.S. Pat. No. 6,657,048.

6BD-25 and 5LAC-23 monoclonal antibodies were produced by culturing the hybridomas in CL-1000 flasks (BD Biosciences, Oakville, ON) with collections and reseeding occurring twice/week. The antibodies were purified according to standard antibody purification procedures with Protein G Sepharose 4 Fast Flow (Amersham Biosciences, Baie d'Urfé, QC).

6BD-25 and 5LAC-23 were compared to a number of both positive (anti-Fas (EOS9.1, IgM, kappa, 20 micrograms/mL, eBioscience, San Diego, Calif.), anti-EGFR (C225, IgG1, kappa, 5 microgram/mL, Cedarlane, Hornby, ON), Cycloheximide (100 micromolar, Sigma, Oakville, ON), NaN_3 (0.1%, Sigma, Oakville, ON)) and negative (107.3 (anti-TNP, IgG1, kappa, 20 microgram/mL, BD Biosciences, Oakville, ON), G155-178 (anti-TNP, IgG2a, kappa, 20 microgram/mL, BD Biosciences, Oakville, ON), MPC-11 (antigenic specificity unknown, IgG2b, kappa, 20 microgram/mL), J606 (anti-fructosan, IgG3, kappa, 20 microgram/mL), IgG Buffer (2%), IgM buffer (2%)) controls in a cytotoxicity assay (Table 1). Breast cancer (MDA-MB-231 (MB-231), MDA-MB-468 (MB-468), MCF-7), colon cancer (HT-29, SW1116, SW620), lung cancer (NCI-H460), ovarian cancer (OVCAR-3), prostate cancer (PC-3), and non-cancer (CCD-27sk, Hs888.Lu) cell lines were tested (all from the ATCC, Manassas, Va.). The Live/Dead cytotoxicity assay was obtained from Molecular Probes (Eugene, Oreg.). The assays were performed according to the manufacturer's instructions with the changes outlined below. Cells were plated before the assay at the predetermined appropriate density. After 2 days, purified antibody or controls were diluted into media, and then 100 microliters were transferred to the cell plates and incubated in a 5 percent CO_2 incubator for 5 days. The plate

was then emptied by inverting and blotted dry. Room temperature DPBS containing $MgCl_2$ and $CaCl_2$ was dispensed into each well from a multi-channel squeeze bottle, tapped three times, emptied by inversion and then blotted dry. 50 microliters of the fluorescent calcein dye diluted in DPBS containing $MgCl_2$ and $CaCl_2$ was added to each well and incubated at 37° C. in a 5 percent CO_2 incubator for 30 minutes. The plates were read in a Perkin-Elmer HTS7000 fluorescence plate reader and the data was analyzed in Microsoft Excel and the results were tabulated in Table 1. The data represented an average of four experiments tested in triplicate and presented qualitatively in the following fashion: 4/4 experiments greater than threshold cytotoxicity (+++), 3/4 experiments greater than threshold cytotoxicity (++), 2/4 experiments greater than threshold cytotoxicity (+). Unmarked cells in Table 1 represent inconsistent or effects less than the threshold cytotoxicity. The chemical cytotoxic agents induced their expected cytotoxicity while a number of other antibodies which were included for comparison also performed as expected given the limitations of biological cell assays. The 6BD-25 antibody demonstrated cytotoxicity in breast, ovarian and colon cancer cell lines selectively, while having no effect on non-transformed normal cells. The 5LAC-23 antibody demonstrated cytotoxicity in the ovarian cancer cell line selectively while also having no effect on non-transformed normal cells. The antibodies 6BD-25 and 5LAC-23 were selective in their activity since not all cancer cell types were susceptible. Furthermore, 6BD-25 and 5LAC-23 demonstrated functional specificity since they did not produce cytotoxicity against non-cancer cell types, which is an important therapeutic factor.

TABLE 1

In Vitro Cytotoxicity of 6BD-25 and 5LAC-23

		Cell Line										
	Antibody	MB-231	MB-468	MCF-7	HT-29	SW1116	SW620	NCI H460	OVCAR	PC-3	CCD 27sk	Hs888 Lu
	6BD-25			+		++			+			
	5LAC-23								++			
Negative Controls	IgM buffer	+										
	IgGI isotype											
Positive Controls	CHX	++	+++	+++	+++	+++	++	++	+++	+++	+++	+++
	NaN_3	+++	+++	+++	+++	++		+++	+++	+++		
	anti-EGFR		+++			+++					++	
	anti-Fas			++					+++	+		

Binding of 6BD-25 to the above-mentioned panel of cancer and normal cell lines was assessed by flow cytometry (FACS). Cells were prepared for FACS by initially washing the cell monolayer with DPBS (without Ca^{++} and Mg^{++}). Cell dissociation buffer (INVITROGEN, Burlington, ON) was then used to dislodge the cells from their cell culture plates at 37° C. After centrifugation and collection, the cells were resuspended in Dulbecco's phosphate buffered saline containing $MgCl_2$, $CaCl_2$ and 25 percent fetal bovine serum at 4° C. (wash media) and counted, aliquoted to appropriate cell density, spun down to pellet the cells and resuspended in staining media (DPBS containing $MgCl_2$ and $CaCl_2$) containing 6BD-25 (unconjugated or conjugated with biotin), 5LAC-23 or control antibodies (isotype control or anti-Fas) at 20 micrograms/mL on ice for 30 minutes. Conjugating 6BD-25 to biotin was performed with biotinylation reagent (Pierce E2-Link Sulfo-NHS-LC-biotin, Rockford, Ill.). The biotinylation reagent was added in 20 times molar excess to 6BD-25 and incubated for 2 hrs at room temperature with shaking. The biotinylated 6BD-25 was then dialyzed overnight against PBS at 4° C. Prior to the addition of Alexa Fluor 488-conjugated secondary antibody (for unconjugated primary antibodies) or streptavidin R-phycoerythrin conjugated secondary antibody (for biotinylated 6BD-25), the cells were washed once with wash media. The appropriate secondary antibody in staining media was then added for 20 minutes. The cells were then washed for the final time and resuspended in staining media containing 1 microgram/mL propidium iodide. Flow cytometric acquisition of the cells was assessed by running samples on a FACScan using the CellQuest software (BD Biosciences, Oakville, ON). The forward (FSC) and side scatter (SSC) of the cells were set by adjusting the voltage and amplitude gains on the FSC and SSC detectors. The detectors for the three fluorescence channels (FL1, FL2, and FL3) were adjusted by running cells stained with purified isotype control antibody followed by the appropriate secondary antibody such that cells had a uniform peak with a median fluorescent intensity of approximately 1-5 units. Live cells were acquired by gating for FSC and propidium iodide exclusion. For each sample, approximately 10,000 live cells were acquired for analysis and the results presented in Table 2. Table 2 tabulated the mean fluorescence intensity fold increase above isotype control and is presented qualitatively as: less than 1.5 (–); 1.5 to 2 (+); 2 to 3 (++); 3 to 10 (+++) and >10 (++++).

Representative histograms of 6BD-25 and 5LAC-23 antibodies were compiled for FIG. 1. Unconjugated 6BD-25 did not initially bind any cell lines tested by FACS. However, after increasing the sensitivity of the assay by conjugating 6BD-25 to biotin, it was demonstrated that a low level of antigen is present on the surface of MDA-MB-231, C-13, OVCA-429 and OV2008 cancer cells. By FACS, 5LAC-23 showed high and specific binding to the colon cancer cell line SW620. For both 6BD-25 and 5LAC-23, this was further evidence that the degree of binding was not necessarily predictive of the outcome of antibody ligation of its cognate antigen, and was a non-obvious finding. This suggested that the context of antibody ligation in different cells was determinative of cytoxicity rather than just antibody binding.

TABLE 2

FACS Analysis of 6BD-25 and 5LAC-23

		Cell Line													
Antibody	Isotype	CCD-27sk	PC-3	NCI-H460	Hs888.Lu	HT-29	SW620	SW1116	MB-231	MB-468	MCF-7	OV2008	C13	OVCA-429	OVCAR-3
6BD-25	IgM, k	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Biotinylated 6BD-25	IgM, k							–	+			+++	+	+	+
5LAC-23	IgM, k	–	–	–	–	–	+++	–	–	–	–				–
anti-Fas (+ control)	IgM, k	++++	+	+++	++++	+++	–	+++	++	+	+++	+++	+++	++	+++

EXAMPLE 2

In Vivo Colon Preventative Tumor Experiments

With reference to the data shown in FIG. 2, 4 to 8 week old, female SCID mice were implanted with 5 million SW1116 human colon cancer cells in 100 microliters saline injected subcutaneously in the scruff of the neck. The mice were randomly divided into 2 treatment groups of 10. On the day prior to implantation 20 mg/kg of 6BD-25 test antibody or buffer control was administered intrapertioneally at a volume of 300 microliters after dilution from the stock concentration with a diluent that contained 500 mM NaCl, 20 mM $Na_2HPO_4.7H_20$ and 20 mM $NaH_2PO_4.H_20$. The antibodies were then administered once per week for a period of 7 weeks in the same fashion.

Tumor growth was measured roughly every 7th day with calipers for up to 16 weeks or until individual animals reached the Canadian Council for Animal Care (CCAC) end-points or day 112. Body weights of the animals were recorded for the duration of the study. At the end of the study all animals were euthanised according to CCAC guidelines.

There were no clinical signs of toxicity throughout the study. Data was analyzed using the independent samples test and significance was determined using the t-test for equality of means. At day 50 (1 day after final treatment), the tumor volume in the 6BD-25 treated group was 54 percent of the buffer control (p=0.001). Delayed growth of the tumor continued past the treatment period. At day 112 (63 days post-treatment), tumor volume in the antibody treatment group was 59 percent of the buffer control (p=0.002). In summary, 6BD-25 antibody treatment reduced tumor burden in comparison to buffer control in a well-recognized model of human colon cancer. These results suggest a potential pharmacologic and pharmaceutical benefit of this antibody (6BD-25) as a therapy in other mammals, including man.

EXAMPLE 3

In Vivo Ovarian Preventative Tumor Experiments

With reference to the data shown in FIGS. 3 and 4, 4 to 8 week old, female SCID mice were implanted with 5 million OVCAR-3 human ovarian cancer cells in 1000 microliters saline injected intraperitoneally. The mice were randomly divided into 2 treatment groups of 10. On the day after implantation 20 mg/kg of 6BD-25 test antibody or antibody buffer was administered intraperitoneally at a volume of 300 microliters after dilution from the stock concentration with a diluent that contained 500 mM NaCl, 20 mM $Na_2HPO_4.7H_20$ and 20 mM $NaH_2PO_4.H_20$. The antibodies were then administered once per week for a period of 9 weeks in the same fashion.

Body weight was measured roughly every 7th day for up to 11 weeks or until individual animals reached the Canadian Council for Animal Care (CCAC) end-points or day 76. Body weights of the animals were recorded for the duration of the study. At the end of the study all animals were euthanised according to CCAC guidelines.

There were no clinical signs of toxicity throughout the study. Body weight was used as a surrogate measure of tumor progression (FIG. 3). Increased body weight is indicative of tumor burden since the weight gain is caused by ascites formation. Significance was determined using the Dunnett's t-test. At day 80 post-implantation (16 days after the end of treatment), mice in the 6BD-25 treatment group had body weights significantly less than the buffer control group (p=0.002). There was also enhanced survival with treatment with 6BD-25 compared to the buffer control (FIG. 4) as determined by the log-rank test. Mice in the control group had a median survival of 87.0 days versus 107.5 days in the 6BD-25 treatment group (p<0.02). Also, all mice in the buffer treatment group had died by day 120 post-implantation (56 days after treatment). In the antibody treatment group, there was still 1 mouse alive at day 250 post-treatment (186 days post-treatment). In summary, 6BD-25 antibody treatment prevented tumor burden in comparison to buffer control in another well-recognized model of human cancer disease. 6BD-25 also enhanced survival in an ovarian xenograft model.

In toto, 6BD-25 is significantly more effective than buffer control in suppressing tumor growth in a preventative tumor xenograft model of colon and ovarian cancer in SCID mice. Treatment with 6BD-25 also showed a survival benefit in a well-recognized model of human ovarian cancer disease suggesting pharmacologic and pharmaceutical benefits of this antibody for therapy in other mammals, including man. Furthermore, the undetectable or low level of antigen expression on the SW1116 and OVCAR-3 cells respectively, illustrates that the level of antigen expression does not necessarily correlate with in vivo efficacy.

All patents and publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

It is to be understood that while a certain form of the invention is illustrated, it is not to be limited to the specific form or arrangement of parts herein described and shown. It will be apparent to those skilled in the art that various changes

may be made without departing from the scope of the invention and the invention is not to be considered limited to what is shown and described in the specification. One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. Any oligonucleotides, peptides, polypeptides, biologically related compounds, methods, procedures and techniques described herein are presently representative of the preferred embodiments, are intended to be exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the appended claims. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the art are intended to be within the scope of the following claims.

What is claimed is:

1. The isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690.

2. A humanized antibody produced from the isolated monoclonal antibody of claim 1.

3. Antigen binding fragments of the isolated monoclonal antibody of claim 1.

4. Antigen binding fragments of the humanized antibody of claim 2.

5. The isolated monoclonal antibody or antigen binding fragments of any one of claims 1, 2, 3, or 4 conjugated with a member selected from the group consisting of toxins, enzymes, radioactive compounds, and hematogenous cells.

6. The isolated hybridoma deposited with the ATCC as Accession Number PTA-5690.

7. A binding assay to determine presence of cancerous cells in a tissue sample selected from a human colon tumor comprising:

providing a tissue sample from said human colon tumor;

providing an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690 or antigen binding fragment thereof; or an antibody conjugate thereof;

contacting said isolated monoclonal antibody or antigen binding fragment thereof or antibody conjugate thereof with said tissue sample; and

determining binding of said isolated monoclonal antibody or antigen binding fragment thereof or antibody conjugate thereof with said tissue sample;

whereby the presence of said cancerous cells in said tissue sample is indicated.

8. A process of isolating or screening for cancerous cells in a tissue sample selected from a human colon tumor comprising:

providing a tissue sample from said human colon tumor;

providing an isolated monoclonal antibody produced by the hybridoma deposited with the ATCC as Accession Number PTA-5690 or antigen binding fragment thereof; or an antibody conjugate thereof;

contacting said isolated monoclonal antibody or antigen binding fragment thereof or antibody conjugate thereof with said tissue sample; and

determining binding of said isolated monoclonal antibody or antigen binding fragment thereof or antibody conjugate thereof with said tissue sample;

whereby said cancerous cells are isolated by said binding and their presence in said tissue sample is confirmed.

* * * * *

EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

WYETH, *et al.*,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	Civil Action No. 07-1492 (JR)
	:	
JON W. DUDAS, Under Secretary of Commerce for Intellectual Property and Director of U.S. Patent and Trademark Office,	:	
	:	
Defendant.	:	

MEMORANDUM OPINION

Plaintiffs here take issue with the interpretation that the United States Patent and Trademark Office (PTO) has imposed upon 35 U.S.C. § 154, the statute that prescribes patent terms. Section 154(a)(2) establishes a term of 20 years from the day on which a successful patent application is first filed. Because the clock begins to run on this filing date, and not on the day the patent is actually granted, some of the effective term of a patent is consumed by the time it takes to prosecute the application. To mitigate the damage that bureaucracy can do to inventors, the statute grants extensions of patent terms for certain specified kinds of PTO delay, 35 U.S.C. § 154(b)(1)(A), and, regardless of the reason, whenever the patent prosecution takes more than three years. 35 U.S.C. § 154(b)(1)(B). Recognizing that the protection provided by these separate guarantees might overlap, Congress has forbidden double-counting: "To the extent that periods of delay attributable to grounds

specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed." 35 U.S.C. § 154(b)(2)(A). Plaintiffs claim that the PTO has misconstrued or misapplied this provision, and that the PTO is denying them a portion of the term Congress has provided for the protection of their intellectual property rights.

Statutory Scheme

Until 1994, patent terms were 17 years from the date of issuance. See 35 U.S.C. § 154 (1992) ("Every patent shall contain . . . a grant . . . for the term of seventeen years . . . of the right to exclude others from making, using, or selling the invention throughout the United States. . . ."). In 1994, in order to comply with treaty obligations under the General Agreement on Tarriffs and Trade (GATT), the statute was amended to provide a 20-year term from the date on which the application is first filed. See Pub. L. No. 103-465, § 532, 108 Stat. 4809, 4984 (1994). In 1999, concerned that extended prosecution delays could deny inventors substantial portions of their effective patent terms under the new regime, Congress enacted the American Inventors Protection Act, a portion of which -- referred to as the Patent Term Guarantee Act of 1999 -- provided for the adjustments that are at issue in this case. Pub. L. No. 106-113, §§ 4401-4402, 113 Stat. 1501, 1501A-557 (1999).

As currently codified, 35 U.S.C. § 154(b) provides three guarantees of patent term, two of which are at issue here. The first is found in subsection (b)(1)(A), the "[g]uarantee of prompt Patent and Trademark Office response." It provides a one-day extension of patent term for every day that issuance of a patent is delayed by a failure of the PTO to comply with various enumerated statutory deadlines: fourteen months for a first office action; four months to respond to a reply; four months to issue a patent after the fee is paid; and the like. See 35 U.S.C. § 154(b)(1)(A)(i)-(iv). Periods of delay that fit under this provision are called "A delays" or "A periods." The second provision is the "[g]uarantee of no more than 3-year application pendency." Under this provision, a one-day term extension is granted for every day greater than three years after the filing date that it takes for the patent to issue, regardless of whether the delay is the fault of the PTO.[1] See 35 U.S.C. § 154(b)(1)(B). The period that begins after the three-year window has closed is referred to as the "B delay" or the "B period". ("C delays," delays resulting from interferences, secrecy orders, and appeals, are similarly treated but were not involved in the patent applications underlying this suit.)

[1] Certain reasons for exceeding the three-year pendency period are excluded, see 35 U.S.C. § 154(b)(1)(b)(i)-(iii), as are periods attributable to the applicant's own delay. See 35 U.S.C. § 154(b)(2)(C).

The extensions granted for A, B, and C delays are subject to the following limitation:

> **(A) In general.**--To the extent that periods of delay attributable to grounds specified in paragraph (1) overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed.

35 U.S.C. § 154(b)(2)(A). This provision is manifestly intended to prevent double-counting of periods of delay, but understanding that intent does not answer the question of what is double-counting and what is not. Proper interpretation of this proscription against windfall extensions requires an assessment of what it means for "periods of delay" to "overlap."

The PTO, pursuant to its power under 35 U.S.C. § 154(b)(3)(A) to "prescribe regulations establishing procedures for the application for and determination of patent term adjustments," has issued final rules and an "explanation" of the rules, setting forth its authoritative construction of the double-counting provision. The rules that the PTO has promulgated essentially parrot the statutory text, see 37 C.F.R. § 1.703(f), and so the real interpretive act is found in something the PTO calls its Explanation of 37 CFR 1.703(f) and of the United States Patent and Trademark Office Interpretation of 35 U.S.C. § 154(b)(2)(A), which was published on June 21, 2004, at 69 Fed. Reg. 34238. Here, the PTO "explained" that:

> the Office has consistently taken the position that if an application is entitled to an adjustment under the three-year pendency provision of 35 U.S.C. § 154(b)(1)(B), the entire period during which the application was pending before the Office (except for periods excluded under 35 U.S.C. § 154(b)(1)(B)(i)-(iii)), and not just the period beginning three years after the actual filing date of the application, is the relevant period under 35 U.S.C. § 154(b)(1)(B) in determining whether periods of delay "overlap" under 35 U.S.C. 154(b)(2)(A).

69 Fed. Reg. 34238 (2004) (emphasis added). In short, the PTO's view is that any administrative delay under § 154(b)(1)(A) overlaps any 3-year maximum pendency delay under § 154(b)(1)(B): the applicant gets credit for "A delay" or for "B delay," whichever is larger, but never A + B.

In the plaintiffs' submission, this interpretation does not square with the language of the statute. They argue that the "A period" and "B period" overlap only if they occur on the same calendar day or days. Consider this example, proffered by plaintiff: A patent application is filed on 1/1/02. The patent issues on 1/1/08, six years later. In that six-year period are two "A periods," each one year long: (1) the 14-month deadline for first office action is 3/1/03, but the first office action does not occur until 3/1/04, one year late; (2) the 4-month deadline for patent issuance after payment of the issuance fee is

1/1/07, but the patent does not issue until 1/1/08, another year of delay attributable to the PTO. According to plaintiff, the "B period" begins running on 1/1/05, three years after the patent application was filed, and ends three years later, with the issuance of the patent on 1/1/08. In this example, then, the first "A period" does not overlap the "B period," because it occurs in 2003-04, not in 2005-07. The second "A period," which covers 365 of the same days covered by the "B period," does overlap. Thus, in plaintiff's submission, this patent holder is entitled to four years of adjustment (one year of "A period" delay + three years of "B period" delay). But in the PTO's view, since "the entire period during which the application was pending before the office" is considered to be "B period" for purposes of identifying "overlap," the patent holder gets only three years of adjustment.

Chevron Deference

We must first decide whether the PTO's interpretation is entitled to deference under Chevron v. NRDC, 467 U.S. 837 (1984). No, the plaintiffs argue, because, under the Supreme Court's holdings in Gonzales v. Oregon, 546 U.S. 243 (2006), and United States v. Mead Corp., 533 U.S. 218 (2001), Congress has not "delegated authority to the agency generally to make rules carrying the force of law," and in any case the interpretation at issue here was not promulgated pursuant to any such authority.

See Gonzales, 546 U.S. at 255-56, citing Mead, 533 U.S. at 226-27. Since at least 1996, the Federal Circuit has held that the PTO is not afforded Chevron deference because it does not have the authority to issue substantive rules, only procedural regulations regarding the conduct of proceedings before the agency. See Merck & Co. v. Kessler, 80 F.3d 1543, 1549-50 (Fed. Cir. 1996).

Here, as in Merck, the authority of the PTO is limited to prescribing "regulations establishing procedures for the application for and determination of patent term adjustments under this subsection." 35 U.S.C. § 154(b)(3)(A) (emphasis added). Indeed, a comparison of this rulemaking authority with the authority conferred for a different purpose in the immediately preceding section of the statute makes it clear that the PTO's authority to interpret the overlap provision is quite limited. In 35 U.S.C. § 154(b)(2)(C)(iii) the PTO is given the power to "prescribe regulations establishing the circumstances that constitute a failure of an applicant to engage in reasonable efforts to conclude processing or examination of an application" (emphasis added) -- that is, the power to elaborate on the meaning of a particular statutory term. No such power is granted under § 154(b)(3)(A). Chevron deference does not apply to the interpretation at issue here.

Statutory Construction

Chevron would not save the PTO's interpretation, however, because it cannot be reconciled with the plain text of the statute. If the statutory text is not ambiguous enough to permit the construction that the agency urges, that construction fails at Chevron's "step one," without regard to whether it is a reasonable attempt to reach a result that Congress might have intended. See, e.g., MCI v. AT&T, 512 U.S. 218, 229 (1994) ("[A]n agency's interpretation of a statute is not entitled to deference when it goes beyond the meaning that the statute can bear.").

The operative question under 35 U.S.C. § 154(b)(2)(A) is whether "periods of delay attributable to grounds specified in paragraph (1) overlap." The only way that periods of time can "overlap" is if they occur on the same day. If an "A delay" occurs on one calendar day and a "B delay" occurs on another, they do not overlap, and § 154(b)(2)(A) does not limit the extension to one day. Recognizing this, the PTO defends its interpretation as essentially running the "period of delay" under subsection (B) from the filing date of the patent application, such that a period of "B delay" always overlaps with any periods of "A delay" for the purposes of applying § 154(b)(2)(A).

The problem with the PTO's construction is that it considers the application delayed under § 154(b)(1)(B) during the

period before it has been delayed. That construction cannot be squared with the language of § 154(b)(1)(B), which applies "if the issue of an original patent is delayed due to the failure of the United States Patent and Trademark Office to issue a patent within 3 years." (Emphasis added.) "B delay" begins when the PTO has failed to issue a patent within three years, not before.

The PTO's interpretation appears to be driven by Congress's admonition that any term extension "not exceed the actual number of days the issuance of the patent was delayed," and by the PTO's view that "A delays" during the first three years of an applications' pendency inevitably lead to "B delays" in later years. Thus, as the PTO sees it, if plaintiffs' construction is adopted, one cause of delay will be counted twice: once because the PTO has failed to meet and administrative deadline, and again because that failure has pushed back the entire processing of the application into the "B" period." Indeed, in the example set forth above, plaintiffs' calendar-day construction does result in a total effective patent term of 18 years under the (B) guarantee, so that - again from the PTO's viewpoint -- the applicant is not "compensated" for the PTO's administrative delay, he is benefitted by it.

But if subsection (B) had been intended to guarantee a 17-year patent term and no more, it could easily have been written that way. It is true that the legislative context -- as

distinct from the legislative history -- suggests that Congress may have intended to use subsection (B) to guarantee the 17-year term provided before GATT. But it chose to write a "[g]uarantee of no more than 3-year application pendency," 35 U.S.C. § 154(b)(1)(B), not merely a guarantee of 17 effective years of patent term, and do so using language separating that guarantee from a different promise of prompt administration in subsection (A). The PTO's efforts to prevent windfall extensions may be reasonable -- they may even be consistent with Congress's intent -- but its interpretation must square with Congress's words. If the outcome commanded by that text is an unintended result, the problem is for Congress to remedy, not the agency.

JAMES ROBERTSON
United States District Judge

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

WYETH, *et al.*,	:	
	:	
Plaintiffs,	:	
	:	
v.	:	Civil Action No. 07-1492 (JR)
	:	
JON W. DUDAS, Under Secretary of Commerce for Intellectual Property and Director of U.S. Patent and Trademark Office,	:	
	:	
Defendant.	:	

ORDER

For the reasons stated in the accompanying memorandum opinion, plaintiffs' motion for summary judgment [12] is **GRANTED** and defendant's motion for summary judgment [16] is **DENIED**. The case is remanded to the agency for further proceedings that are consistent with this opinion.

JAMES ROBERTSON
United States District Judge